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International application number: PCT/US05/010005

International filing date: 23 March 2005 (23.03.2005)

Document type: Certified copy of priority document

Document details: Country/Office: US

Number: 60/555,448

Filing date: 23 March 2004 (23.03.2004)

Date of receipt at the International Bureau: 13 June 2005 (13.06.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



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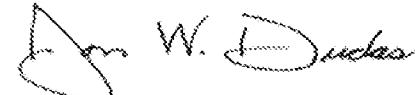
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032304  
1671 U.S. PTO

PTO/SB/16 (10-01)

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This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No.

EI193107628US

22264  
60/555448  
U.S. PTO  
032304**INVENTOR(S)**

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
John, A. Baudouin Guilford	Porco Gerard Jones	Chestnut Hill, MA Allston, MA Canton, MA

 Additional inventors are being named on the \_\_\_\_\_ separately numbered sheets attached hereto**TITLE OF THE INVENTION (500 characters max)**Synthesis of the Aglaine Skeleton by Photogeneration and Dipolar Cycloaddition of  
Oxidopyryliums Derived from 3-Hydroxyflavanones

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**ENCLOSED APPLICATION PARTS (check all that apply)** Specification Number of Pages

3

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 Drawing(s) Number of Sheets

13

 Other (specify)

\_\_\_\_\_

 Application Data Sheet. See 37 CFR 1.76**METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT** Applicant claims small entity status. See 37 CFR 1.27.FILING FEE  
AMOUNT (\$) A check or money order is enclosed to cover the filing fees The Commissioner is hereby authorized to charge filing  
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United States Government. No. Yes, the name of the U.S. Government agency and the Government contract number are: \_\_\_\_\_

Respectfully submitted,

SIGNATURE

Date

03/23/2004

TYPED or PRINTED NAME John A. Porco, Jr.

REGISTRATION NO.  
(if appropriate)  
Docket Number:

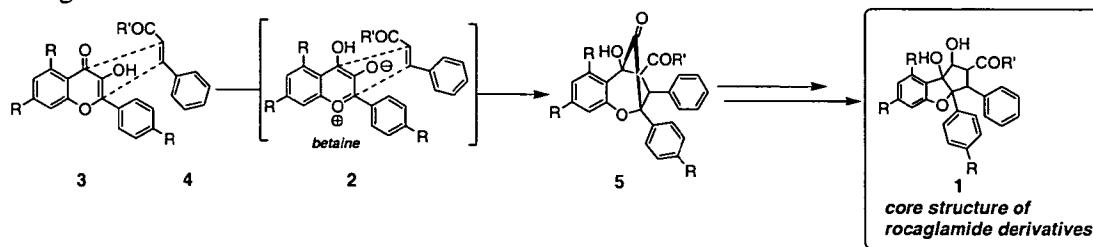
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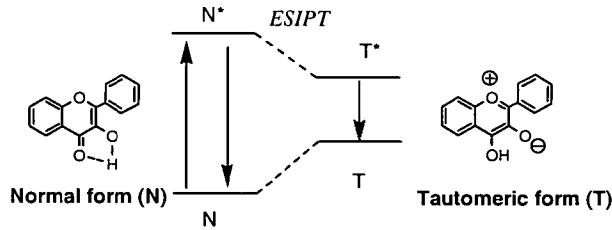
This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C. 20231.

Our laboratory has recently embarked on a synthetic chemistry project involving the synthesis of the core structure **1** of the rocaglamides and related antitumor natural products (**Scheme 1**). Our essential approach involves generation of the oxidopyrylium species **2** from a 3-hydroxyflavone derivative **3** and subsequent dipolar cycloaddition to cinnamate derivatives **4** to afford the aglain skeleton **5** and thence rocaglamide framework **1** after rearrangement of **5** and further modifications.



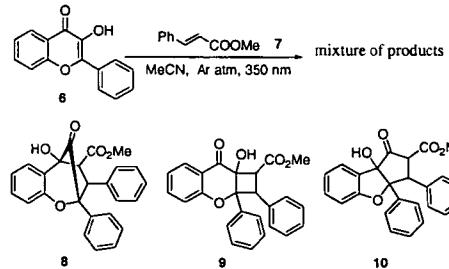
**Scheme 1:** Biomimetic approach of the rocaglamide core structure

Literature reports have documented excited state intramolecular proton transfer (ESIPT) of 3-hydroxyflavone (3-HF) derivatives leading to the formation of the requisite oxidopyrylium betaine-type dipoles **2**. The overall ESIPT process (**Figure 1**) involves generation of a putative tautomeric form of 3-HF where the proton of the hydroxyl group at C3 position migrates to the ketone group at C4 position to yield a oxidopyrylium species (tautomeric form **T**). Although ESIPT processes of 3-HF derivatives have been reported in the literature to produce excited state species such as **T**, to our knowledge there are no reports of chemical reactions *e.g.* cycloaddition processes with these potentially reactive intermediates.



**Figure 1:** ESIPT and fluorescence emission in 3HF

Our initial efforts toward understanding the cycloaddition reactivity of the oxidopyrylium species **T** was focused on model studies with commercially available 3-hydroxyflavone (**Figure 2**). Photoirradiation of **6** in the presence of the dipolarophile methyl cinnamate **7** (5 equivalents) in acetonitrile as solvent produced a mixture of products (**Figure 2**). According to spectroscopic data (<sup>1</sup>H NMR and IR) and X-ray analysis (**Figure 3**), the major compound produced in 56 % chemical yield was confirmed to be the [3+2] cycloadduct **8**.



**Figure 2:** Possible cycloadducts obtained from the cycloaddition between 3HF and methyl cinnamoyl ester

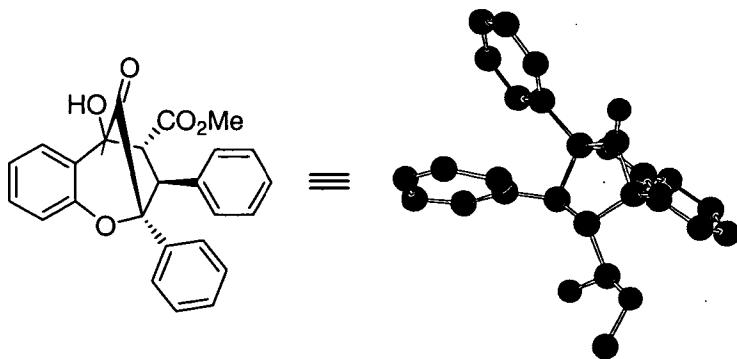
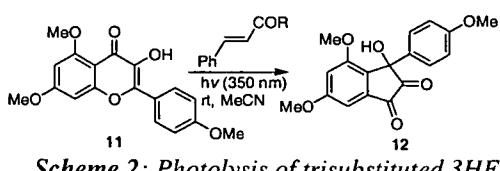


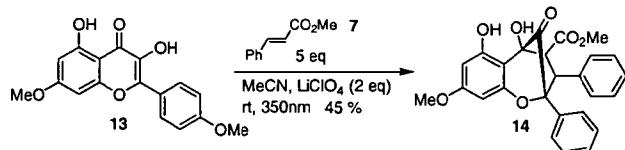
Figure 3: X-ray analysis of cycloadduct 8



Scheme 2: Photolysis of trisubstituted 3HF

Attempted cycloaddition using **11** failed to yield any cycloaddition product but instead afforded the byproduct 3-aryl-3-hydroxy-1,2-indandione **12** (Scheme 2). In contrast, photoirradiation of the 5-OH derivative **13** at 350 nm (MeCN, rt) did not afford any

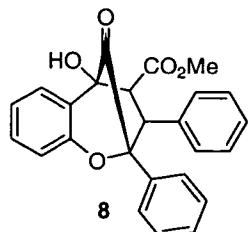
perceptible photorearrangement product. When **13** was photoirradiated in the presence of methyl cinnamate as dipolarophile, no cycloadduct was formed. However, initial experiments indicated that inclusion of different metal cations (e.g. LiClO<sub>4</sub>, Zn (OTf)<sub>2</sub>, and Y(OTf)<sub>3</sub>) facilitated formation of cycloadduct **14** (proposed structure, regio- and stereoselectivity not known), Scheme 4. This indicates a specific potential requirement for both a 5-OH substituent and metal cation in order to potentially generate photochemically and react an oxidopyrylium from a 3-hydroxyflavanone such as **13**.



Scheme 4: possible cycloadduct obtained using *Li(ClO<sub>4</sub>)*

**Summary:** In preliminary experiments, we have found that the parent 3-hydroxyflavanone undergoes photoirradiation in the presence of a dipolarophile to produce an apparent cycloadduct resulting from 1,3 dipolar cycloaddition. However, in preliminary studies employing more highly oxygenated 3-hydroxyflavanone derivatives, we have found that it may be necessary to utilize a 5-hydroxy flavanone derivative in conjunction with a metal salt additive for the cycloaddition process to successfully occur.

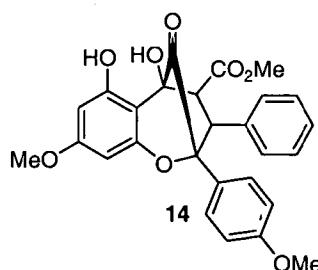
## Experimental procedure



### **General procedure for preparation of aglain derivative 8.**

To a test tube (16 x 100 mm) was charged with commercially available 3-hydroxyflavone **6** (Indofine Chemical Company) (400 mg, 1.7 mmol) and methyl cinnamate **7** (650 mg, 4 mmol) and 8 mL of anhydrous acetonitrile. After degassing using Ar, the mixture was submitted to irradiation (350 nm, Hanovia UV lamp with uranium filter), at rt for 2 hours. The solution was concentrated *in vacuo* to afford a yellow oil. Purification *via*

flash chromatography (60:40 hexanes/EtOAc) afforded 370 mg (0.94 mmol, 56 %) of aglain derivative **10** as a colorless solid. IR  $\nu_{\text{max}}$  (film): 3452.43, 3060.19, 3033.01, 2939.81, 1766.99, 1735.92, 1607.77, 1584.47, 1483.50, 1452.43  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.34-76.82 (14 H, m), 4.631 (1 H, d,  $J$  = 8.4 Hz), 3.645 (1 H, d,  $J$  = 8.4 Hz), 3.606 (3 H, s), 3.57 (1 H, s); HRMS (Cl/NH<sub>3</sub>) m/z calculated for  $\text{C}_{25}\text{H}_{20}\text{O}_5$  400.1311 found 401.1357 (M+H).



### **General procedure for preparation of aglain derivative 14.**

To a test tube (16 x 100 mm) charged with 5-hydroxyflavonanone **13** (20 mg, 0.064 mmol), methyl cinnamate **7** (155 mg, 0.92 mmol), and lithium perchlorate (13.5 mg, 0.12 mmol) was added 2 mL of anhydrous acetonitrile. After degassing using Ar, the mixture was submitted to irradiation (350 nm) at rt for 17 hours. The organic

layer was washed once with 2 mL of water and 2 mL of saturated brine. After drying over  $\text{MgSO}_4$  and concentrated *in vacuo* to afford a yellow oil. Purification *via* flash chromatography (60:40 hexanes/EtOAc) afforded 7 mg (0.015 mmol, 45 %) of aglain **14** as a yellow solid. IR  $\nu_{\text{max}}$  (film): 3378.64, 2955.34, 2920.39, 2846.60, 1778.64, 1712.62, 1623.30, 1580.58, 1518.45, 1491.26, 1429.13, 1254.37, 1145.63  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.15 (1 H, s), 7.28 (2 H, d,  $J$  = 9.2 Hz), 7.04-7.00 (3 H, m), 6.80-6.78 (2 H, m), (6.635, 2d,  $J$  = 9.2 Hz), 6.06 (2H, m), 4.56 (2 H, d,  $J$  = 8 Hz), 4.31 (1 H, s), 3.72 (3H, s), 3.69 (3H, s), 3.67 (3H, s), 3.51 (2H, d,  $J$  = 8 Hz), HRMS (Cl/NH<sub>3</sub>) m/z calculated for  $\text{C}_{27}\text{H}_{24}\text{O}_8$  476.1471 found 476.9583.

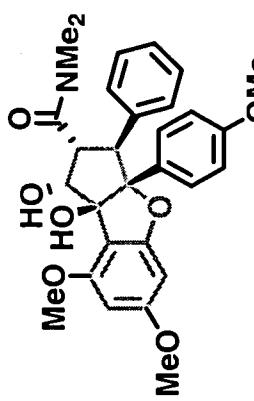
# I) Background and significance

## A) Origin and biological activities

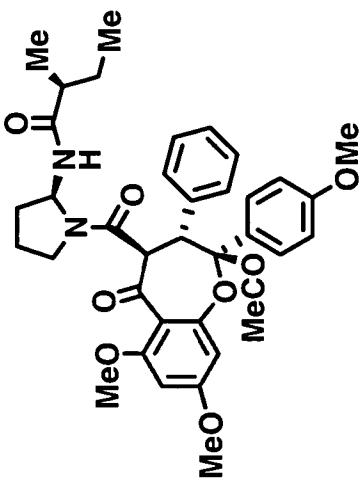
### Rocaglamide derivatives

#### Biological activities:

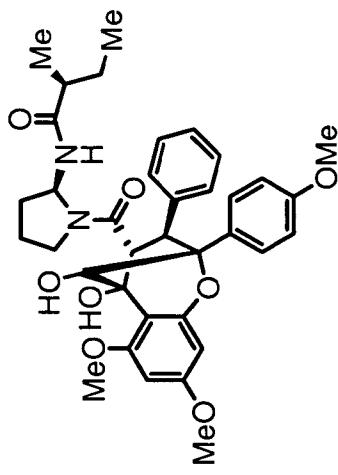
- Anti-inflammatory
- Insecticide
- Cytostatic activities against human cancer cell lines



### Forbaglin derivatives

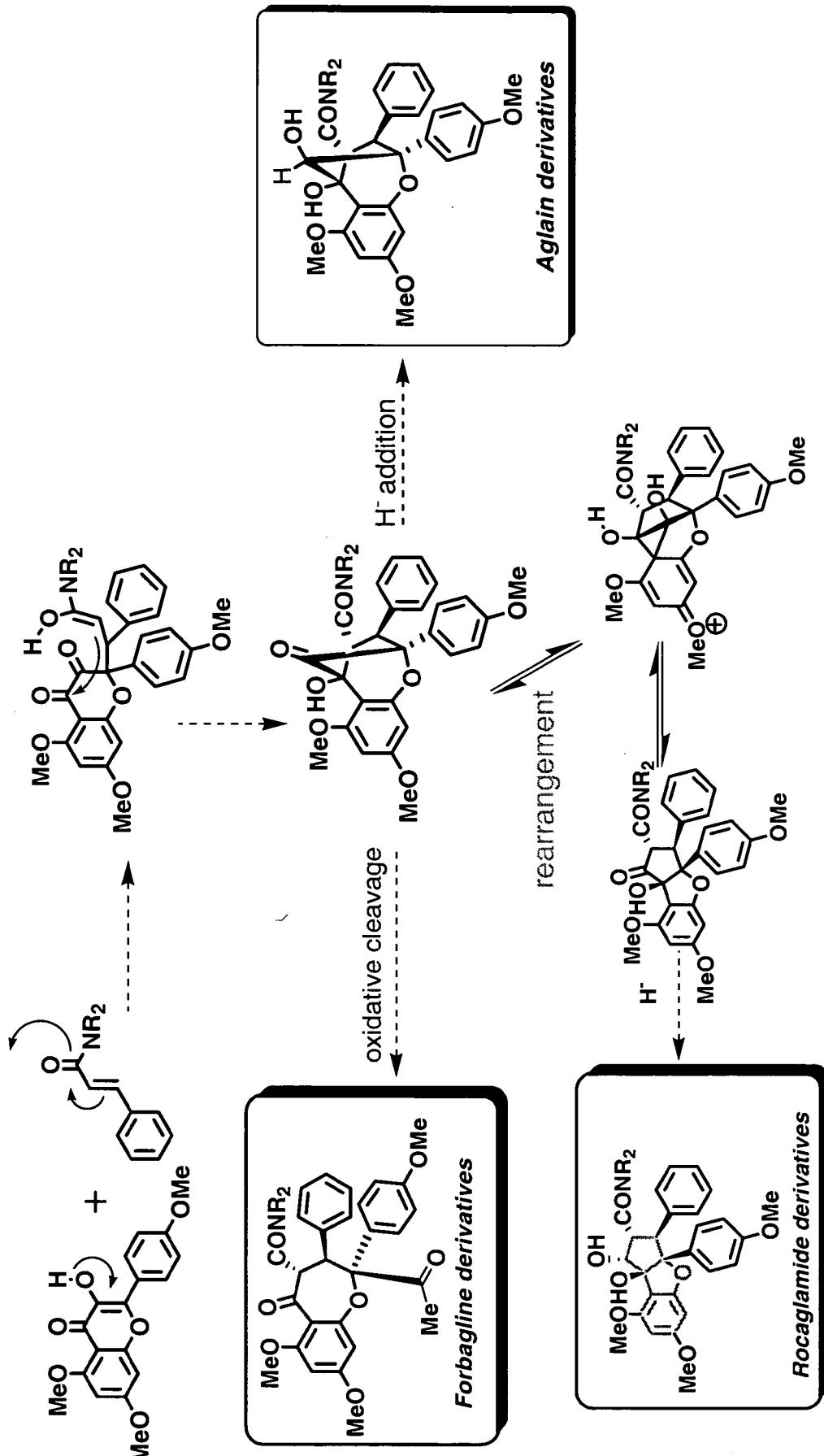


### Aglain derivatives



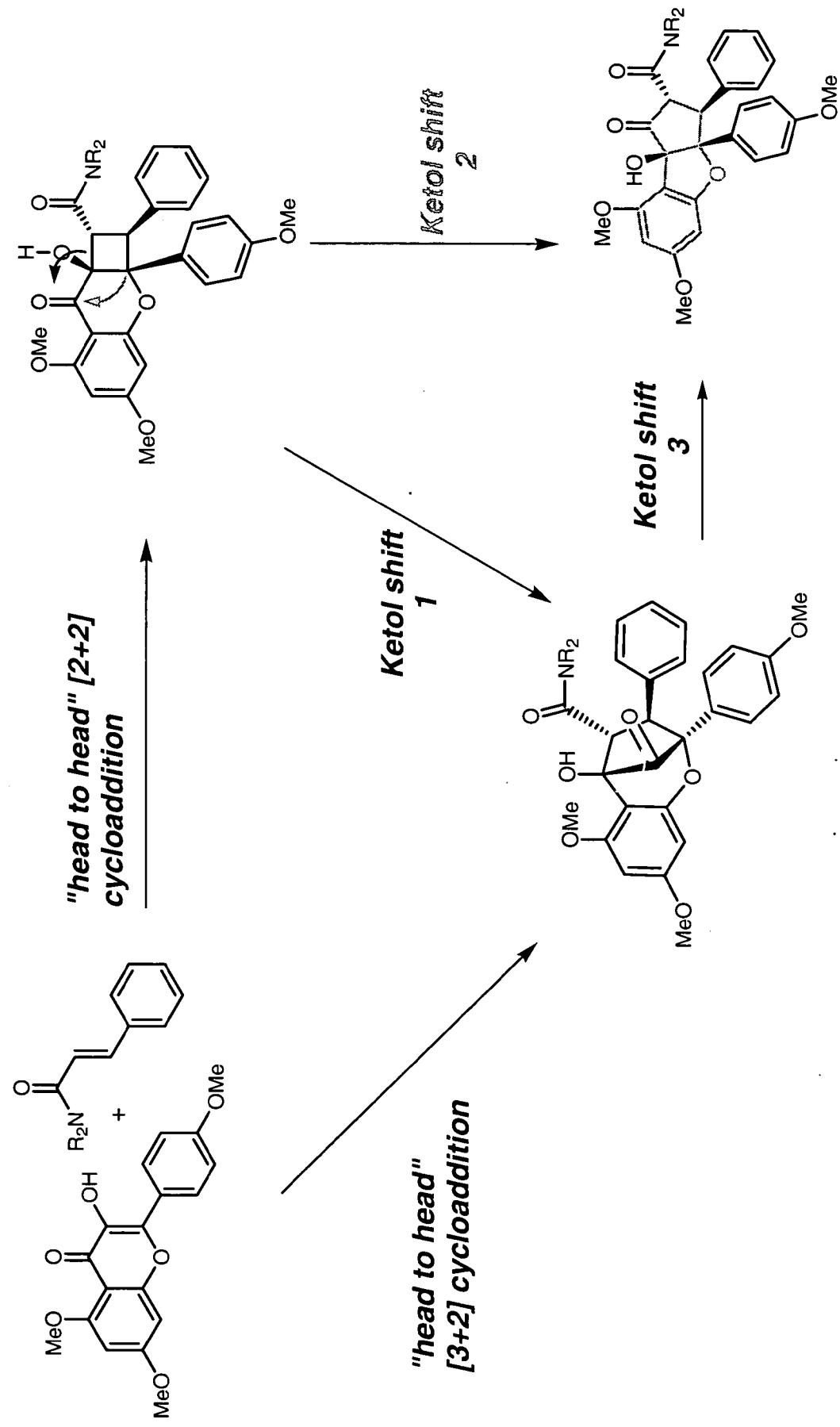
# I) Background and significance

## B) Proposed biosynthesis of rocaglamide derivatives (Proksch)



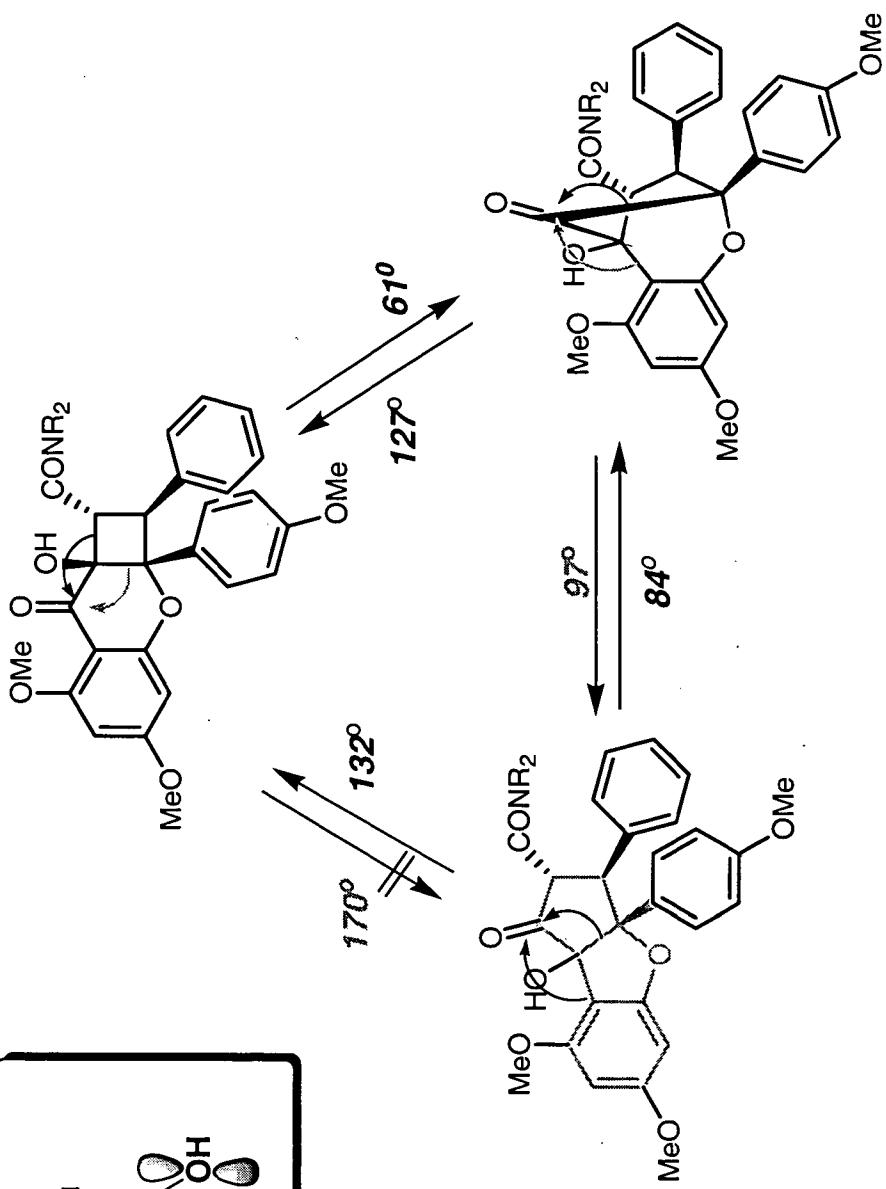
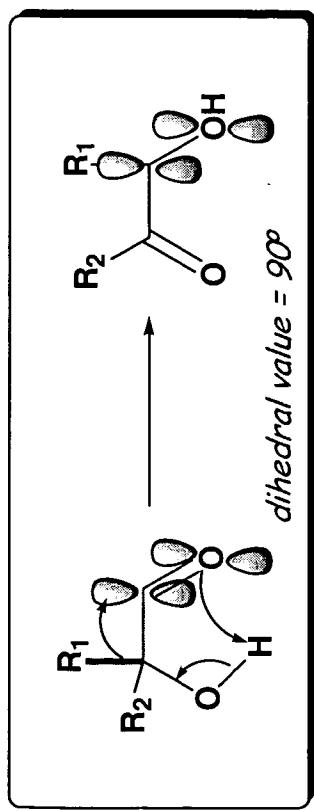
### III) *Proposed biomimetic synthesis*

A) *Biomimetic synthesis of rocaglamide derivatives based on [2+2] and [3+2] cycloaddition (Porco group)*



## II) *Proposed biomimetic synthesis*

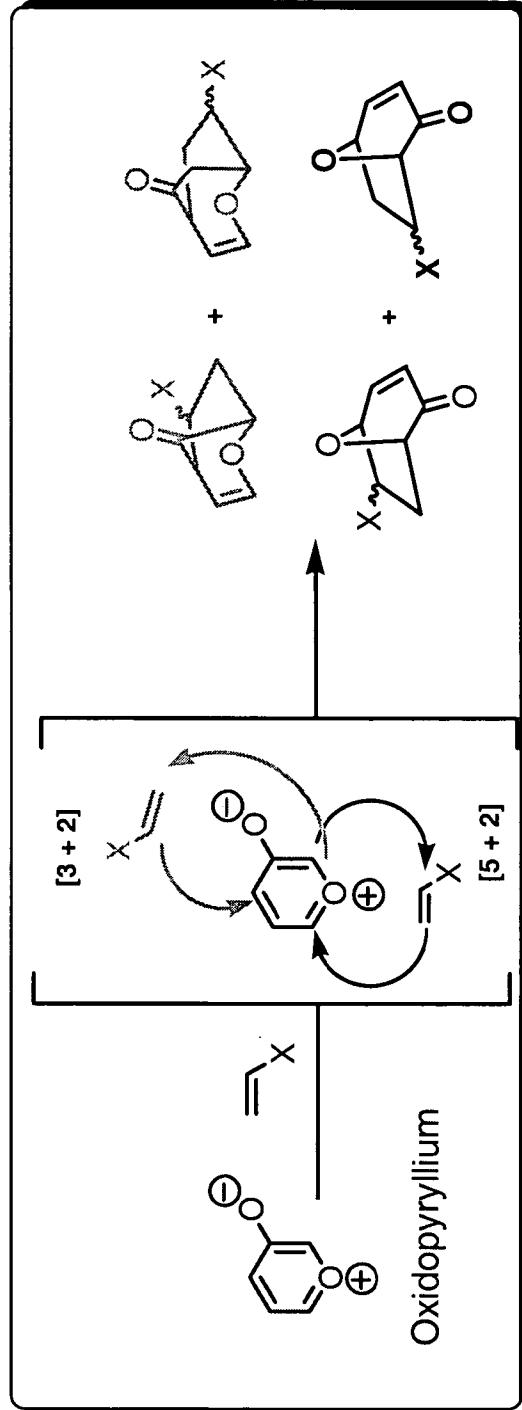
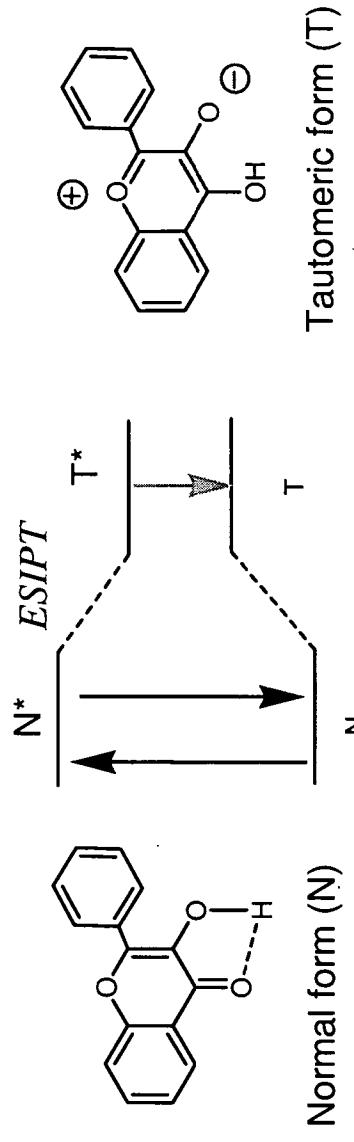
### B) *Ketol shift equilibrium between the different ring systems*



Dihedral angle values has been obtained after energy minimization of the different ring system using molecular mechanics (PC Spartan)

### III) Our Proposed biomimetic synthesis

#### C) Excited State Intramolecular Proton Transfer (ESIPT)

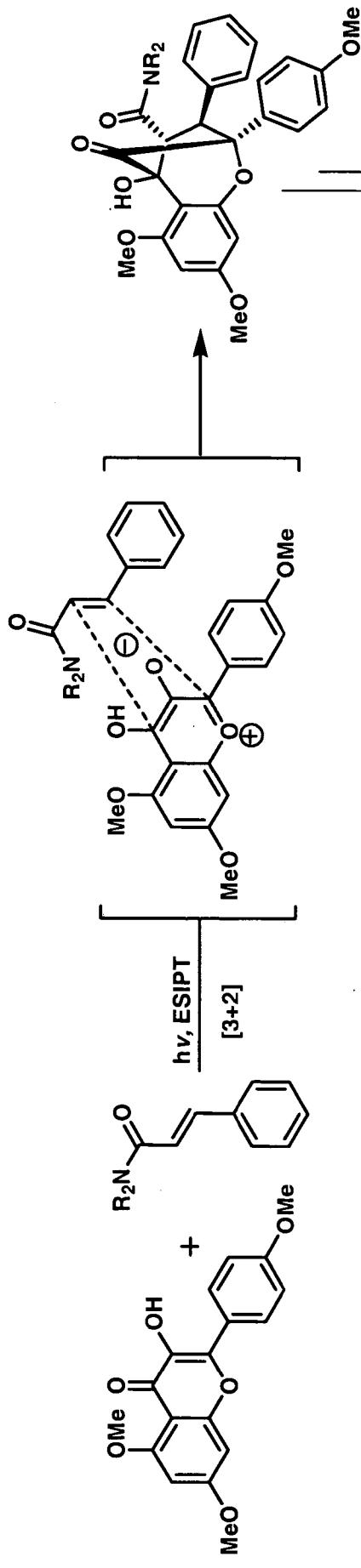


Excited State Intramolecular Proton Transfer of 3-hydroxyflavones :

(a) Samanta, A.; Mandal, P. K.; *J. Phys. Chem. A*, **2003**, *107*, 6334-6339. (b) Demchenko, A. P. *J. Phys. Chem. A*, **2003**, *107*, 4211-4216. (c) Rastogi, R.; Sharma, N.; Jain, S. K.; *Spectrochim Acta, Part A*, **2001**, *57*, 299-308

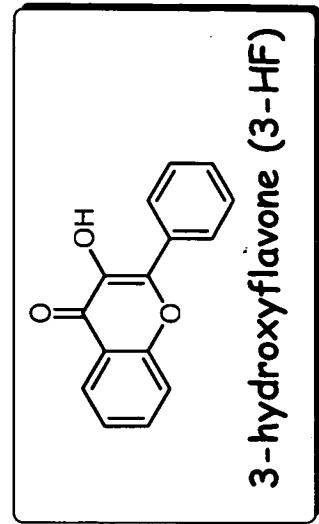
### III) Proposed biomimetic synthesis

#### C) [3+2] cyclization



#### Issues :

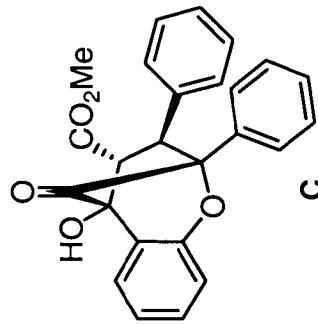
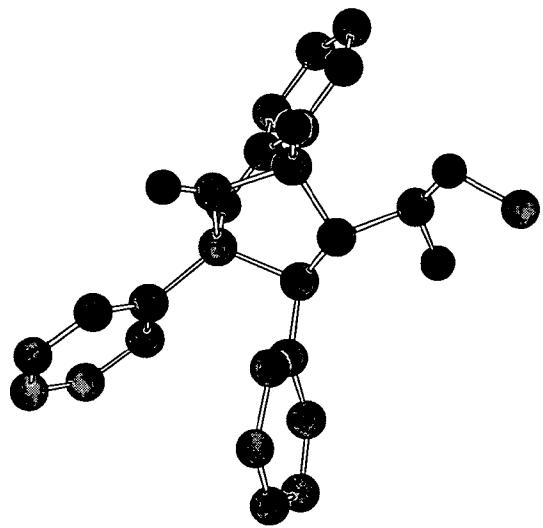
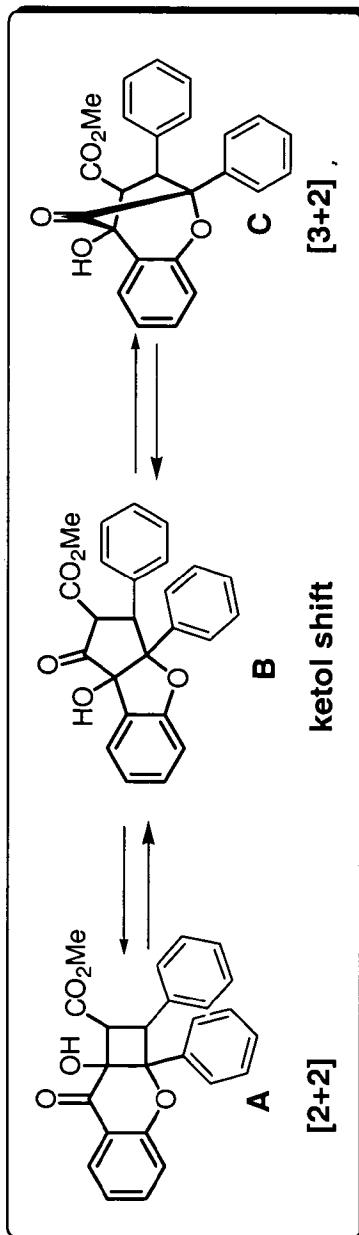
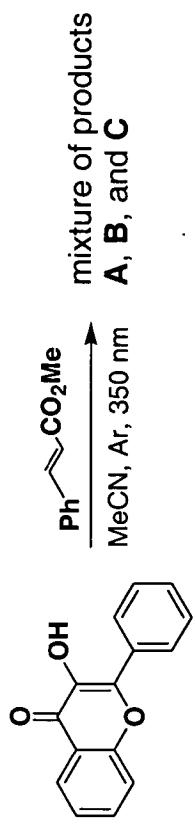
- Lifetime of the phototautomer species
- Wavelength
- Solvent
- Regioselectivity and/or stereochemistry (controlled by FMO theory)



⇒ We began our study with 3-HF as a model system

### III) Preliminary result

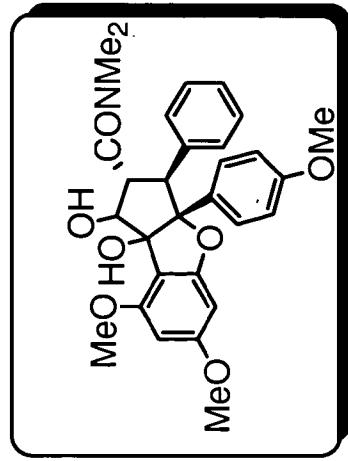
#### A) Model study : 3-hydroxyflavone (3HF)



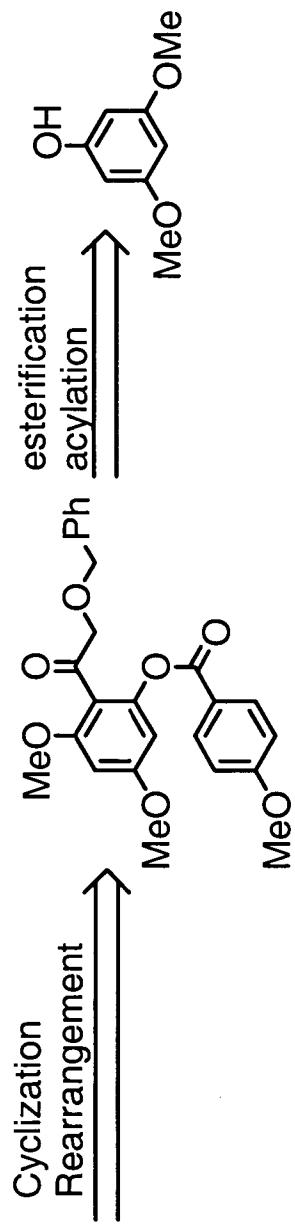
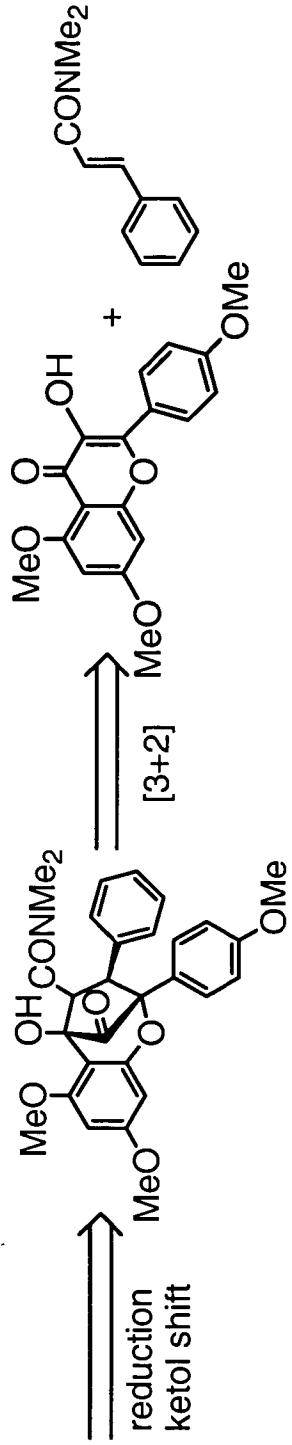
X ray analysis

### III) Preliminary result

#### B) Retrosynthesis of rocaglamide

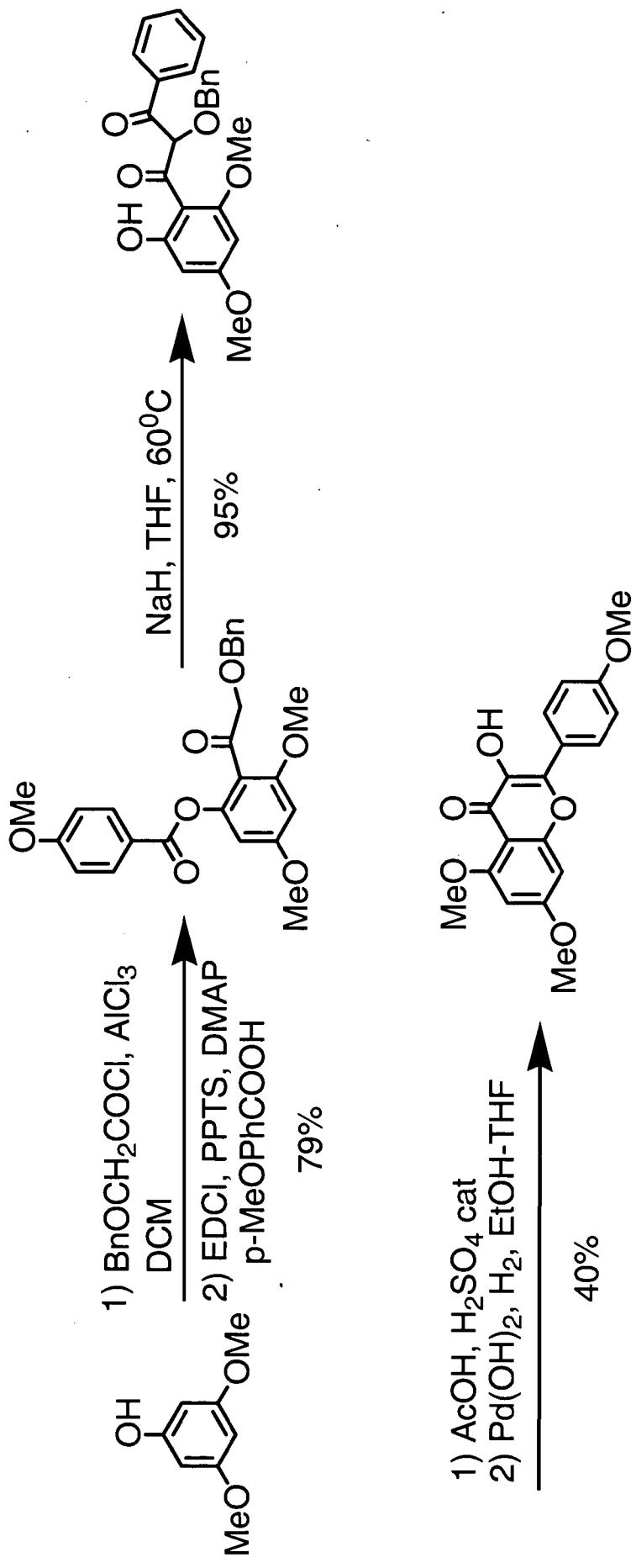


*Rocaglamide*



### III) Preliminary result

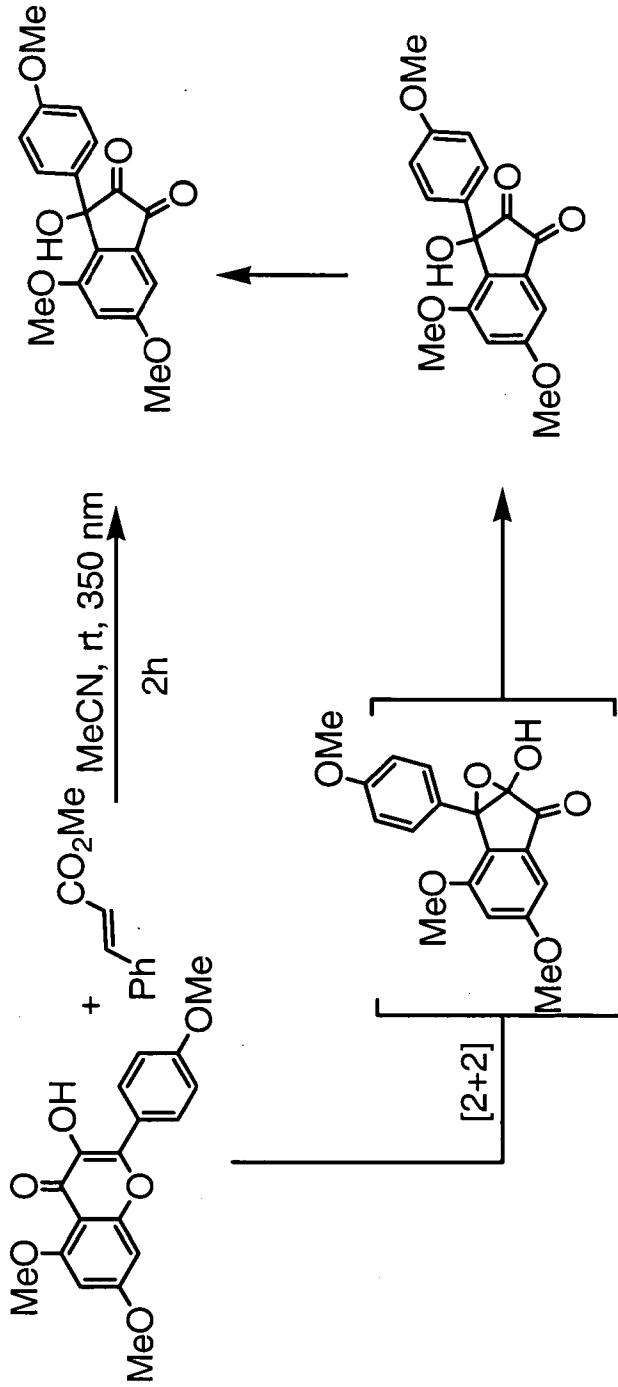
#### B) Synthesis of a trisubstituted 3-hydroxyflavone



For a related sequence, see: Tanaka, H.; Stohlmeyer, M. M.; Wandless, T. J.; *Tetrahedron Lett.* **2000**, *41*, 9735-9739

### III) Preliminary result

#### C) Attempted cycloaddition using trimethoxy flavone



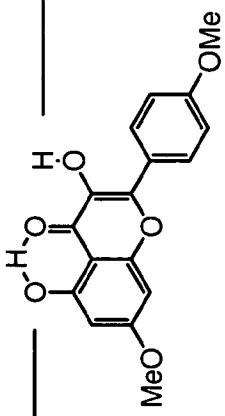
⇒ Several conditions (254 and 350 nm, solvent (MeCN, MeOH) and dipolarophile have been screened but no cycloadduct has been observed in initial experiments

For information on this photorearrangement, see: Matsuura, T.; Takemoto, T.; Nakashima, R.; *Tetrahedron*, 1973, 29, 3337-3340

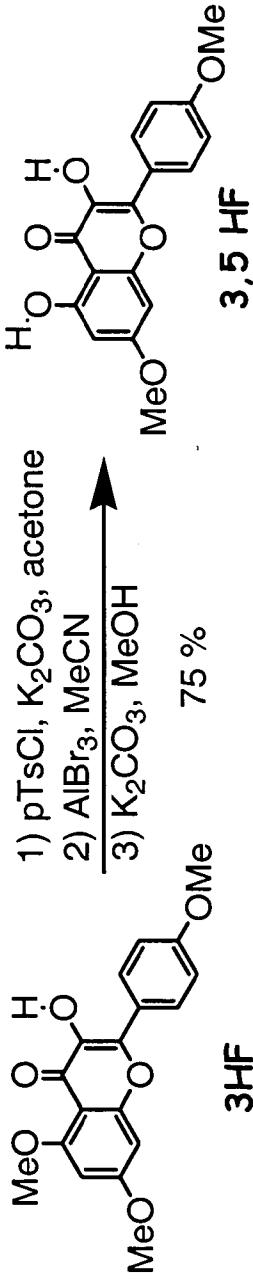
### III) Preliminary result

#### D) Substrate modifications and early results

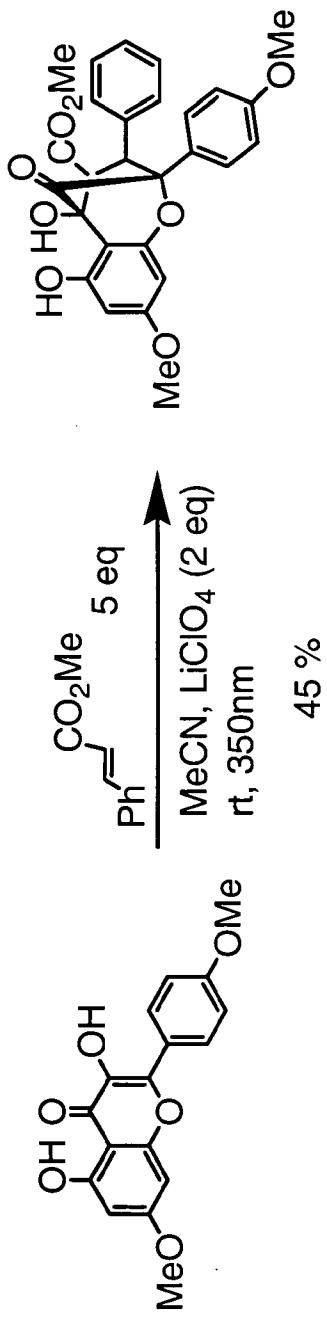
Intramolecular quenching through H-bond between 5-OH and 4-CO help for photoresistance (avoid formation of photorearrange product)



Additive could help not only to keep photoresistance of 3HF but also increase ESIPT process

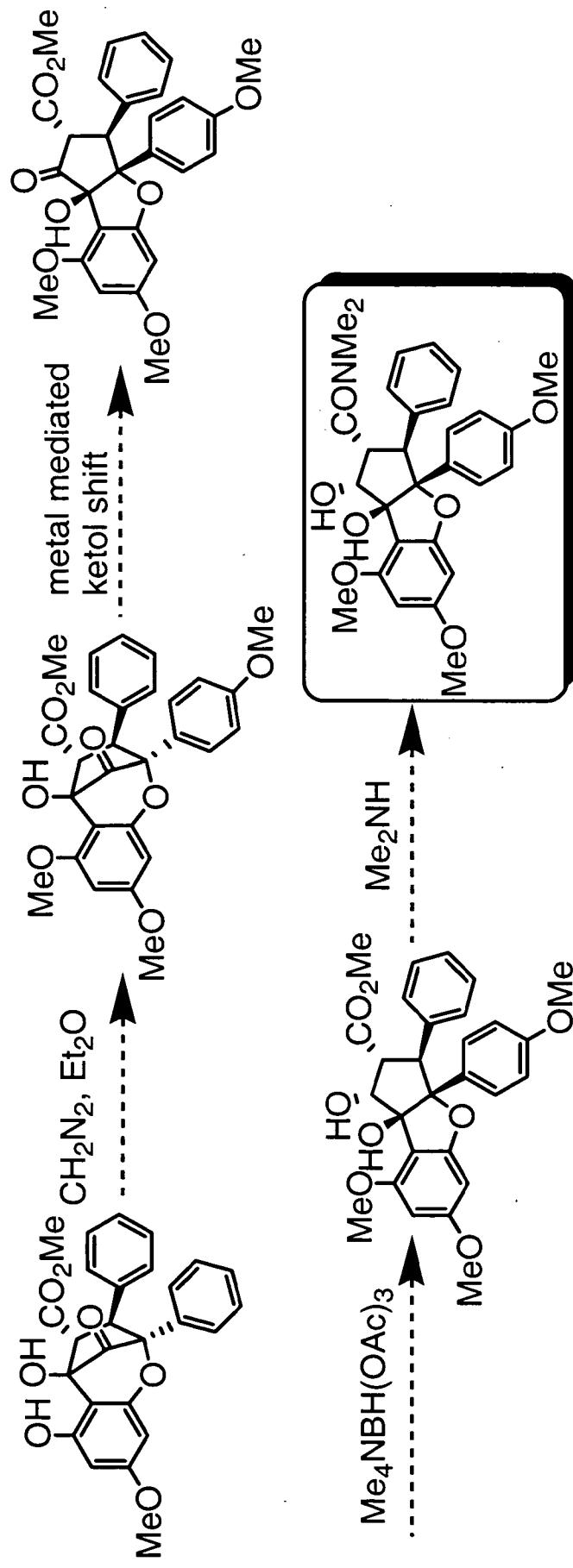


#### Preliminary results (proposed regioselectivity)



## IV) Future Work

### A) Completion of the synthesis of *rocaglamide*



screening for ketol shift:  
Ni(II), Sm(II), BF<sub>3</sub>, Al(III)

*Rocaglamide*

Application of ketol shift rearrangement: Brunner, H.; Stohr, F.; *Eur. J. Org. Chem.* 2000, 2777-2786

## IV) Summary

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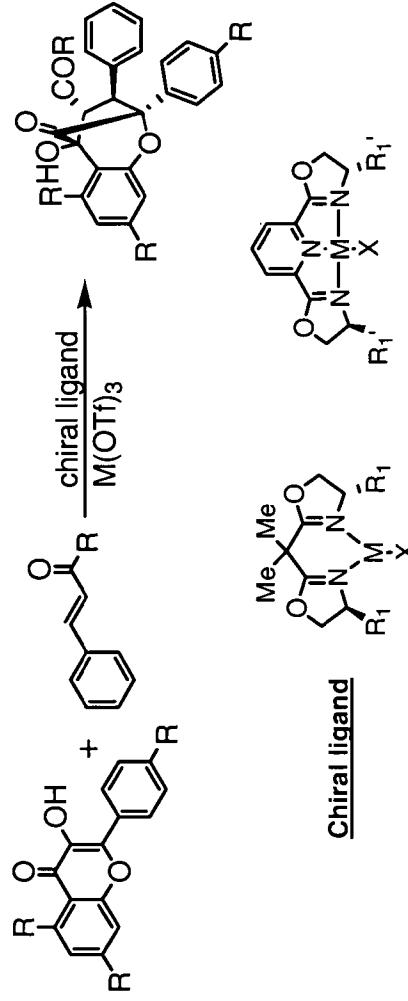
This poster outlines:

A plan towards the total synthesis of rocaglamide and related analogues

⇒ Formation of a 3HF pyryllium species will be promoted *via* a proton transfer reaction

⇒ Trapping of the dipole by cinnamic derivatives through a [3+2] cycloaddition

- Future plans include development of an asymmetric variant of the dipolar Cycloaddition using chiral lewis acid



R<sub>1</sub>: Ph, *i*-Pr, *t*-Bu

R: Ph, *i*-Pr, *t*-Bu